In the Specification

Please substitute the following paragraph on page 4, beginning at line 15:

1) Resolve *dl-threo*-methylphenidate by the procedure described in the Example of PCT/GB97/00185 (International Publication No. WO 97/27176): Ditoluoyl-D-tartaric acid (5.033 g, 12.4 mmol) was suspended in a solution of 2% methanol in acetone (10 ml), and a solution of *threo*-methylphenidate (2.9 g, 12.4 mmol) in the same solvent (10 ml) was added. The solution was gently warmed to reflux whereupon all the reagents dissolved. The solution was immediately cooled and crystals began to form. The solution was allowed to stand at 4°C for 17 hours and was then filtered. The crystals were washed with acetone (3 x 15 ml) and dried *in vacuo* to yield the ditoluoyl-D-tartrate salt of *d-threo*-methylphenidate (3.516 g, 44.3% by weight; corresponding to 97%.ee *d-threo* methylphenidate, as determined by chiral HPLC after salt cracking). The mother liquors were dried *in vacuo* to yield the ditoluoyl-D-tartrate salt of *l-threo*-methylphenidate as a solid, dry form (4.508 g, 50.5% yield, 88% ee).

The ditoluoyl-D-tartrate salt of *d-threo*-methylphenidate (3.486 g), obtained as described above, was suspended in 2% methanol in acetone, and warmed to c. 40°C and cooled. This did not dissolve the solid which was stirred at room temperature for 24 hours. The suspension was filtered, the solid washed with acetone (10 ml) and dried *in vacuo*, to yield diastereomerically pure material (3.209 g, 92% recovery, corresponding to >99% ee *d-threo*-methylphenidate).

Repeating this protocol using isopropanol: methanol as the solvent, gave the same salt, on initial crystallization, enriched in at least 98%. Reslurrying increased this.

Remarks

Claims 1-8 are pending in the subject application and are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested. Applicants gratefully acknowledge the Examiner's indication that the finality of the Office Action dated September 24, 2002 has been withdrawn.

As an initial matter, Applicants again note that a Claim of Priority Under 35 USC §119 was included with the filing materials when the subject application was submitted to the Patent Office on August 10, 2001. In accordance with MPEP 201.14(b), Applicants reaffirmed their claim to foreign priority and requested that the foreign priority applications from the parent application, U.S. application Serial No. 08/792,415 (hereinafter the '415 application), be made of record in the subject application. A copy of the Claim of Priority Under 35 USC §119 filed with the subject application on August 10, 2001 is attached with this Amendment for the Examiner's convenience. Applicants note that certified copies of Great Britain priority applications Serial No. 9602174.6 and Serial No. 9618836.2 were submitted to the Patent Office in the '415 application on June 4, 1997. Applicants further note that the Examiner in the '415 application acknowledged receiving all of the certified copies of the foreign priority documents on the Summary page of the Office Action dated November 27, 1998. Accordingly, Applicants respectfully request acknowledgment in the next Communication from the Patent Office of their claim to foreign priority and that the foreign priority documents have been made of record by the Examiner in the subject application.

Claims 1-8 are rejected under 35 USC §103(a) as obvious over Shaflee (1969) in view of Barry (1993) or Miller (abstract (1980) and U.S. Patent No. 4,254,261); and over Shaflee (1969) in view of Barry (1993) or Miller (abstract (1980) and U.S. Patent No. 4,254,261) further in view of Rometsch (U.S. Patent No. 2,957,880); and over Shaflee (1969) in view of Barry (1993) or Miller (abstract (1980) and U.S. Patent No. 4,254,261) further in view of Rometsch (U.S. Patent No. 2,957,880) and Jacques (1981) supplemented with Harris (U.S. Patent No. 6,242,464). In the outstanding Office Action, the Examiner seems to indicate that the Miller references teach the racemization of a molecule with two chiral centers into all four stereoisomers. Applicants respectfully traverse each of these grounds of rejection.

As an initial matter, Applicants note the subject application was filed after November 29, 1999 but is entitled to the benefit of the filing date of September 12, 1996 of U.S. provisional application Serial No. 60/021,135. The Harris patent (U.S. Patent No. 6,242,464) was filed January 22, 1997 and claims priority to a provisional application filed March 21, 1996. Thus, U.S. Patent No. 6,242,464 only qualifies as prior art against the subject application under 35 USC §102(e). U.S. Patent No. 6,242,464 and the subject application were owned by, or subject to an obligation of assignment to, the same entity. Applicants' undersigned representative hereby states that, at the time the invention of the subject application was made, the subject application and U.S. Patent No. 6,242,464 were commonly owned by, or subject to an obligation of assignment to, Chiroscience Limited. The subject application is a continuation application of U.S. application Serial No. 08/792,415. The inventors assigned their rights in the 08/792,415 application in February of 1997 to Chiroscience Limited. U.S. Patent No. 6,242,464 was owned by Chiroscience Limited at the time the subject invention was made. Accordingly, under 35 USC §103(c), the Harris patent cannot be used in a rejection of the claimed invention under 35 USC §103(a). Reconsideration and withdrawal of the rejection of the claims over Shaflee (1969) in view of Barry (1993) or Miller (abstract (1980) and U.S. Patent No. 4,254,261) further in view of Rometsch (U.S. Patent No. 2,957,880) and Jacques (1981) supplemented with Harris (U.S. Patent No. 6,242,464) is respectfully requested.

In regard to the rejection of the claims over those combinations of the cited references without the Harris patent, Applicants respectfully maintain that the claimed invention is **not** obvious, regardless of whether the references are taken alone or in combination. Applicants acknowledge that the primary reference relied upon by the Examiner, the Shaflee reference, discloses methylphenidate; however, Shaflee does not teach or suggest methods for racemizing methylphenidate (or any other single molecule with two chiral centers) at both of the chiral centers in the molecule, *i.e.*, wherein every one of the four possible stereoisomers of methylphenidate is produced. Nor do any of the other references cited in the §103 rejections. Applicants' utilization of a means for racemizing methylphenidate at both chiral centers of the molecule is a critical aspect of the invention that the Examiner apparently fails to appreciate or take into consideration when applying the references cited under the rejections.

The Examiner acknowledged in the Office Action dated September 28, 2001 that the Shaflee reference does not teach a racemization step. Prior to Applicants' invention, there was no teaching or suggestion in the art of being able, and the ordinarily skilled artisan did not have motivation, to racemize methylphenidate at both of the chiral centers of the molecule. Applicants maintain that none of the references cited by the Examiner under these rejections teach or suggest a single molecule that has two chiral centers within the molecule itself. In making the rejections under §103, no evidence or references have been presented or cited by the Patent Office which teach or suggest, with the required reasonable expectation of success, how an ordinarily skilled artisan might effect racemization of a single enantiomer of methylphenidate at both chiral centers of the molecule. The fact that methylphenidate was known in the art and that it was known that methylphenidate contained two chiral centers does not put the ordinarily skilled artisan in possession of a means for racemizing a single enantiomer of methylphenidate to produce all four stereoisomers of methylphenidate in the absence of a teaching in the art of a means to effect such a racemization. If the Examiner disagrees with Applicants' assessment, then Applicants respectfully request that the Examiner indicate, with specificity, where in the cited references one can find a teaching or suggestion of a means for racemizing a single enantiomer of methylphenidate (or even some other molecule of similar chemical structure and having two chiral centers) that would have predictably produced all four possible stereoisomers.

In regard to the Examiner's comments regarding the teachings of the Miller references, Applicants respectfully assert that the compound, homopyrrolidone carboxylic acid (HPCA), that is racemized as described in the Miller references has only **one chiral center** (see, for example, column 1, lines 59-60, of the Miller patent). The Miller patent specifically states that HPCA exists as "the S-enantiomer, the R-enantiomer, and the R,S-racemate." It is clear from the disclosure in the Miller references that HPCA has one chiral center and, therefore, exists as only two (not four) enantiomers: R-HPCA and S-HPCA. Dehydroabietylamine (DAA), which is used in the Miller patent to form a salt with HPCA, may also have a chiral center but that is not the compound which is racemized. Moreover, the formation of a salt between HPCA and DAA is not equivalent to a single molecule having two chiral centers and which can be racemized to form four separate, distinct stereoisomers. As noted above, it is only HPCA that is racemized and it only has a single chiral center. The Miller

abstract does not contain any disclosure beyond what is present in the Miller patent; the abstract merely discloses racemizing an enantiomer of HPCA. Thus, the Miller references do not teach or suggest an individual molecule that has two chiral centers formed by the structural arrangement of the atoms of the molecule, nor do the Miller references teach or suggest means for racemizing a single enantiomer of a molecule with two chiral centers to give all four different stereoisomers. It is only the disclosure in the subject application that teaches racemization of an enantiomer of methylphenidate into all four stereoisomers.

Applicants respectfully maintain that the substrates disclosed in the Barry reference have only one chiral center within the molecule itself. Thus, any racemization that may be taught in the Barry reference is racemization of a molecule with a single chiral center, and not racemization of a single molecule with two chiral centers as provided in Applicants' claimed invention. Accordingly, Applicants respectfully maintain that the Barry reference does not teach or suggest anything concerning a means for racemizing a molecule, such as methylphenidate, having two chiral centers so as to produce all four possible stereoisomers from a single enantiomer.

Applicants respectfully assert that any assumption that the use of racemization methods described in the cited references will result in racemization at both chiral centers of methylphenidate is incorrect. Applicants respectfully maintain that one need look no farther than the cited Rometsch patent as evidence that the prior art does not teach or suggest means to racemize methylphenidate at both of its chiral centers. Example 6 of the Rometsch patent discloses epimerisation of methylphenidate with base; however, only one of the two chiral centers of the methylphenidate molecule is racemized, which thereby results in a mixture of diastereomers (*i.e.*, less than all of the four possible stereoisomers of methylphenidate are produced). The results disclosed in the Rometsch patent clearly indicate that when one started with a single enantiomer of methylphenidate, both chiral centers of methylphenidate were not racemized. Using the nomenclature of the Rometsch patent, the racemizations described at column 2, lines 19-27, of the patent are:

1) $a_1 + a_2 \rightarrow a_1 + a_2 + b_1 + b_2$,

2) $a_1 \rightarrow a_1 + b_1$

and

3) $a_2 \rightarrow a_2 + b_2$.

In reaction (1), the starting materials include two different enantiomers (a_1 and a_2) of methylphenidate and, therefore, racemization is not proceeding from a single enantiomer starting material. In reaction (2) and (3), only two of the four possible enantiomers result from each reaction. It is clear from the Rometsch patent disclosure that these conversions involve "scrambling" at only one (not both) chiral center of the methylphenidate molecule. Column 2, lines 25-27, of the Rometsch patent confirms this, wherein it is stated that "... **contrary to expectation** the rearrangement in this process takes place at only one of the two asymmetrical carbon atoms." (emphasis added). Thus, it is explicitly acknowledged in the Rometsch patent disclosure that racemization of an enantiomer of methylphenidate did not result in racemization at both of the chiral centers of the molecule and, therefore, did not produce all four possible stereoisomers from a single enantiomer of methylphenidate. Moreover, all racemization processes described in the Rometsch patent are in the a→ b direction. In contrast to the teachings of the Rometsch patent, the present invention goes in the opposite direction (b→ a); using the Rometsch nomenclature, either b_1 is racemized (at both chiral centers) or b_2 is racemized (at both chiral centers), to give all of a_1, a_2, b_1, and b_2 (*i.e.*, the four possible enantiomers).

In the Office Action, the Examiner seems to suggest that all four stereoisomers of methylphenidate are produced from the method of the Rometsch patent and concludes with the explanation that the Rometsch patent "did not *name* all four enantiomers ...." However, the Examiner does not point out where in the Rometsch patent there is a teaching of all four enantiomers of methylphenidate, be they named or unnamed in the patent text. Applicants respectfully assert that the Examiner is merely speculating that all four enantiomers of methylphenidate were produced by the methods disclosed in the Rometsch patent. Consideration of the molecular structure of methylphenidate would suggest to the ordinarily skilled artisan that one of the two chiral centers of the molecule can be racemized much more easily than the other, thereby leading to the production of fewer than all four possible stereoisomers. This is clearly supported by the experimental results disclosed in the Rometsch patent. Accordingly, Applicants respectfully assert that the cited Rometsch patent teaches away from Applicants' claimed invention in that the Rometsch patent specifically discloses that racemization of methylphenidate occurs at only one of the two chiral centers of the molecule and, therefore, Applicants ability to racemize methylphenidate at both chiral

centers to thereby produce all four stereoisomers from a single enantiomer of methylphenidate is nowhere suggested.

One possible interpretation of the Examiner's statement in the instant Office Action that "just because the prior art such as Rometsch did not *name* all four enantiomers, does not mean the racemization using the same acid would not give all four enantiomers," is that the Examiner is suggesting that the production of all four stereoisomers was inherent in the process disclosed in the Rometsch patent. If the Examiner is asserting that production of all four stereoisomers was inherent in the Rometsch process, Applicants respectfully assert that reliance on the inherent properties of a product or process is only appropriate in regard to anticipation rejections made under 35 USC §102 where a single reference is cited. Matters of inherency do not apply to obviousness rejections under 35 USC §103. Moreover, it is well established in patent law that the presence of an inherent property or effect must be grounded on more than speculation, it must be a certainty and a person of ordinary skill in the art must necessarily recognize its presence. *Scaltech Inc. v. Retec/Tetra L.L.C.*, 48 USPQ2d 1037 (Fed. Cir. 1998), revised and reissued, 51 USPQ2d 1055, 1059 (Fed. Cir. 1999) ("Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient to establish inherency.") (emphasis added); *Crown Operations International Ltd. v. Solutia Inc.*, 62 USPQ2d 1917 (Fed. Cir. 2002). Applicants respectfully assert that it was not a certainty that the process disclosed in the Rometsch patent would produce all four stereoisomers of methylphenidate. Applicants note that the Examiner has not provided any reasoning, explanation or evidence that the production of all four stereoisomers was inherent in the methods of the Rometsch patent. As noted above, the Examiner is speculating that all four stereoisomers resulted from the Rometsch patent methods. The Examiner also seems to suggest that Applicants must prove, by way of a "*factual* comparison," that the methods of the Rometsch patent do not result in production of all four stereoisomers of methylphenidate. Applicants respectfully assert that the burden of providing an evidentiary basis for asserting that the production of all four stereoisomers of methylphenidate was inherent in the methods of the Rometsch patent lies with the Patent Office, and not with Applicants. *In re Grose*, 201 USPQ 57 (CCPA 1979).

Also attached with this Amendment is a Declaration of Dr. Hooshang S. Zavareh Under 37 CFR 1.132. In his Declaration, Dr. Zavareh points out that racemization of an enantiomer of methylphenidate so that all four enantiomers are obtained requires abstraction of a proton. Dr. Zavareh states that it is, therefore, surprising that an acid, as is recited in the claimed method, could be used to racemize a single enantiomer of methylphenidate into all four possible enantiomers. Applicants respectfully request that Dr. Zavareh's Declaration be considered and made of record in the subject application.

In addition, Applicants have also submitted with this Amendment a published article by Mahavir Prashad entitled "Approaches to the Preparation of Enantiomerically Pure (*2R,2'R*)-(+)-*threo*-Methylphenidate Hydrochloride" (2001, *Adv. Synth. Catal.*, Vol. 343, No. 5, pp. 379-392). Applicants note that this article was published after the effective filing date of the subject application. The article indicates that the author, Dr. Prashad, is a senior fellow and group leader in the Process R&D section of Chemical and Analytical Development at the Novartis Institute for Biomedical Research. The article is a review article and concerns methods for producing enantiomerically pure methylphenidate. Applicants would like to bring to the attention of the Examiner that portion of the article at page 383, section 4, a portion of which is reprinted below:

> A resolution process is more attractive and economical if the undesired enantiomer can be recycled via racemization. However, in the case of methylphenidate, such a racemization is challenging because there are two stereogenic centers which have to be epimerized. A method to affect the racemization at both stereogenic centers has been demonstrated by refluxing a solution of (*2R,2'R)-threo*-methylphenidate (1) with propionic acid in toluene to afford a mixture of four stereoisomers in roughly equal proportions (citing published International Application No. WO 97/28124).

Dr. Prashad references published International Application WO 97/28124 as the first publication to describe a successful means for the complete racemization of a single enantiomer of methylphenidate into all four stereoisomers. No other references are cited as teaching or suggesting a means for racemization of single enantiomer methylphenidate into all four possible enantiomers. Published application WO 97/28124 application, a copy of which is attached with this Amendment, is the corresponding international filing of the subject application. Applicants note that the subject

application and the WO 97/28124 application have identical inventorship, claim priority to the same British patent applications, and have the same disclosure in the specification. Dr. Zavareh's Declaration and the article by Dr. Prashad provide further evidence as to the non-obviousness of Applicants' claimed invention.

As the Examiner is aware, it is well established in patent law that in order to support a *prima facie* case of obviousness, a person of ordinary skill in the art must find both the suggestion of the claimed invention, and a reasonable expectation of success in making that invention, solely in light of the teachings of the prior art. *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Applicants respectfully assert that the cited references do not teach or suggest the claimed invention, nor do they provide the requisite reasonable expectation of success; therefore, the claimed invention is not obvious over the cited references. Should the Examiner disagree and maintain some or all of the rejections, then Applicants respectfully request the Examiner in any subsequent Action to specifically and precisely point out where and how the cited references teach or suggest each and every element of Applicants' claimed method. Applicants have specifically addressed each of the references cited by the Examiner in this and previous Responses in the subject application and the parent application and have explained in detail the failings of each of those references. Similarly, if the Examiner disagrees with Applicants' assertions as to the teachings of each of the cited references, then Applicants respectfully request that the Examiner clearly and specifically point out any difference the Examiner has with Applicants' interpretation of the teachings of each of the cited references. If the Examiner does not specifically indicate disagreement with Applicants' assertions concerning the teachings of each of the cited references or rebut Applicants' assertions, then Applicants must assume that the Examiner agrees with the assertions made by Applicants concerning the teachings of the cited references. The burden of establishing a *prima facie* case of obviousness of a claimed invention is on the Patent Office. If a *prima facie* case of obviousness cannot be established or supported, then the obviousness rejection is improper and the rejection must be withdrawn. In view of the remarks presented herein, reconsideration and withdrawal of the rejections under 35 USC §103(a) is respectfully requested.

Claim 1 is rejected under 35 USC §112, first paragraph, on the ground that the subject specification must be amended to incorporate the disclosure described in the example in International

Application No. PCT/GB97/00185 regarding resolution of *dl-threo*-methylphenidate. The Examiner asserts that this is "essential material" and incorporation by reference of essential material is limited to U.S. patents only. Applicants respectfully assert that the material disclosed in PCT/GB97/00185 is not essential material and is offered merely as an example of one process that can be used to resolve *threo*-methylphenidate. Applicants respectfully stress that any suitable resolution process can be used to resolve the *dl-threo*-methylphenidate; the claims are not limited to any particular resolution process. However, in an effort to expedite prosecution of the subject application to completion, Applicants have amended the subject specification to include the text of the example from Application No. PCT/GB97/00185. Applicants respectfully assert that no new matter is added by the Amendment.

Also, under this rejection, the Examiner expresses concern that International Application No. PCT/GB97/00185 discloses the resolution of *dl-threo*-methylphenidate into a ditoluoyl-D-tartrate salt of *d-threo*- and *l-threo*-methylphenidate and seems to suggest that such a resolution process cannot be used in Applicants' claimed process and questions how one would racemize such salts. Applicants again stress that the resolution process disclosed in International Application No. PCT/GB97/00185 is but a single example of a resolution process that can be used to resolve *dl-threo*-methylphenidate into the *d-threo* and *l-threo* enantiomers; other methods of resolution are known in the art and include, for example, use of 1,1'-binaphthyl-2,2'-diyl hydrogen phosphate as described in Patrick *et al.* (1987), *The Journal of Pharmacology and Experimental Therapeutics* 241:152-158, already of record in the subject application. As is indicated in International Application No. PCT/GB97/00185, methods for converting the resolving agent salt of methylphenidate to the hydrochloride salt via salt exchange procedures are well known in the art. Moreover, the free base of methylphenidate can be obtained from a salt via salt cracking methods, which are also well known in the art. Thus, one can readily prepare a base of methylphenidate from a ditoluoyl-D-tartrate salt of a methylphenidate enantiomer. As the Examiner is undoubtedly aware, there is no requirement that a specification teach that which is well known in the art. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986) citing *Lindemann Maschinenfabrik v. American Hoist and Derrick*, 221 USPQ 481 (Fed. Cir. 1984), (". . . a patent need not teach, and preferably omits, what is well known in the art.").

In regard to racemization of the methylphenidate enantiomers, the subject application teaches means for racemization at page 4, lines 5-11, of the subject specification. Reference in the protocol disclosed at page 4 of the subject specification to "the experiment above" means the experiment described at page 4, lines 5-11, of the subject specification. The method disclosed at page 4, lines 5-11, of the subject specification produces "all 4 stereoisomers of methylphenidate in roughly equal proportions." (see lines 10-11 of the subject specification). Thus, there is proper and adequate written description in the subject specification for both the resolution of *dl-threo*-methylphenidate and the racemization of the unwanted enantiomer, *e.g.*, *l-threo*-methylphenidate and, therefore, Applicants' remarks regarding the criticality of the two chiral centers in methylphenidate are completely relevant to the patentability of the claimed invention.

In view of the remarks presented herein, reconsideration and withdrawal of the rejection under 35 USC §112, first paragraph, is respectfully requested.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

Doran R. Pace
Patent Attorney
Registration No. 38,261
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: 2421 N.W. 41st Street, Suite A-1
Gainesville, FL 32606-6669

DRP/sl

Attachments: copy of the Claim of Priority Under 35 USC §119; Declaration of Dr. Hooshang S. Zavareh Under 37 CFR 1.132; copy of article by Mahavir Prashad (2001); copy of published International Application No. WO 97/28124.